Cost-effectiveness of vaccination strategies to protect older adults

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Chapter 7

Cost-effectiveness of quadrivalent versus trivalent influenza vaccine in the United States

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Abstract

Background: Designed to overcome influenza B mismatch, new quadrivalent influenza vaccines (QIVs) contain one additional B strain compared with trivalent influenza vaccines (TIVs).

Objective: To examine the expected public health impact, budget impact, and incremental cost-effectiveness of QIV versus TIV in the United States.

Methods: A dynamic transmission model was used to predict the annual incidence of influenza over the 20-year-period of 2014 to 2034 under either a TIV program or a QIV program. A decision tree model was interfaced with the transmission model to estimate the public health impact and the cost-effectiveness of replacing TIV with QIV from a societal perspective. Our models were informed by published data from the United States on influenza complication probabilities and relevant costs. The incremental vaccine price of QIV as compared with that of TIV was set at US $5.40 per dose.

Results: Over the next 20 years, replacing TIV with QIV may reduce the number of influenza B cases by 27.2% (16.0 million cases), resulting in the prevention of 137,600 hospitalizations and 16,100 deaths and a gain of 212,000 quality-adjusted life-years (QALYs). The net societal budget impact would be US $5.8 billion and the incremental cost-effectiveness ratio US $27,411/QALY gained. In the probabilistic sensitivity analysis, 100% and 96.5% of the simulations fell below US $100,000/QALY and US $50,000/QALY, respectively.

Conclusions: Introducing QIV into the US immunization program may prevent a substantial number of hospitalizations and deaths. QIV is also expected to be a cost-effective alternative option to TIV.

1. Introduction

Seasonal influenza is a viral infectious disease caused by influenza type-A (H1N1 and H3N2) viruses or influenza type-B viruses (Yamagata and Victoria). Surveillance data show that B strains represent on average 24% of viral isolates in the United States (US) and from the 2001-2002 season to the present, both B lineages have cocirculated each season at varying levels and with no regularity [1]. In the US, the average annual public health burden of seasonal influenza (types A and B) is estimated at 24,000 deaths and 95,000 hospital admissions; however, in severe seasons, this can increase to 49,000 and 270,000, respectively [2,3]. Also, the economic burden of influenza is significant. Annual influenza-related medical costs in the United States have been estimated at US $10 billion and productivity costs at US $16 billion [4]. Seasonal vaccination against influenza is regarded as the most effective strategy to prevent influenza disease [5]. Traditional influenza vaccines are trivalent, containing strains of two influenza A subtypes (one of each H1N1 and H3N2) and one strain of an influenza B lineage (Victoria or Yamagata), according to recommendations of the World Health Organization. However, over the decade 2001 through 2012, mismatches between the circulating B lineage and the B strain of the vaccine occurred in 5 of the 10 seasons in the US because of the cocirculation of both influenza B lineages [1]. Two recent meta-analysis have demonstrated that TIV offers suboptimal protection when there is a mismatch between circulating influenza B and B vaccine strains (B-lineage vaccine efficacy is 71%–77% when TIV influenza B is lineage matched and 46%–49% when mismatched) [6,7].

To address the problem of influenza B matching, quadrivalent influenza vaccines (QIVs) were developed and licensed in the US market in 2012 [8]. In addition to strains of the two influenza A subtypes, QIVs contain strains from both type-B lineages (Victoria and Yamagata). The US Centers for Disease Control and Prevention (CDC) estimated that QIV might have prevented on average 340,000 influenza cases, 2,700 hospitalizations, and 170 deaths within the seasons 2001/02 to 2008/09 [9]. Moreover, two economic evaluations demonstrated that the cost-effectiveness of shifting from TIV to QIV was favorable [10–12]. However, published economic evaluations of QIV versus TIV in the US so far are based on static models. The static approach assumes a constant risk of infection and does not incorporate the indirect protection that the successfully immunized proportion of the population provides to those individuals who are still susceptible, by reducing the risk of transmission (herd effects). Dynamic models simulate disease transmission by taking into account contact patterns between humans and the risk of transmission per contact, which allows the model to account for herd effects [13]. Because influenza vaccination impacts disease transmission, the dynamic approach can be regarded as the more appropriate approach to quantify the epidemiological and economic impact of replacing TIV by QIV [14]. The aim of this study was to assess the cost-effectiveness of QIV versus TIV for seasonal vaccination in the US on the basis of a dynamic modeling approach.

2. Methods

2.1. Overview

The cost-effectiveness model uses an age-structured dynamic transmission model to estimate the impact of QIV over TIV in terms of clinical outcomes, costs, and health effects. Clinical outcomes included outpatient visits, hospitalizations, and deaths. Costs were assessed from the third-party payer's (TPP's) perspective, considering reimbursed direct medical costs only, as well as from the societal perspective, which also accounts for out-of-pocket-paid over-the-counter medication and indirect costs due to productivity losses. Final outcomes of the study were incremental costs per quality-adjusted life-year (QALY) gained and incremental costs per life-year (LY) gained.

2.2. Model Design

The dynamic transmission model developed by Crepey et al. [15] was used to estimate age-stratified numbers of symptomatic influenza B cases under the QIV and TIV strategies. The model is a variation on the compartmental SEIR model, where individuals can be susceptible to infection (S), exposed but not infectious (E), infectious (I), or recovered (R) from an infection and therefore immune for a certain time period. A vaccination compartment was added to account for individuals effectively protected from infection by vaccination. The model accounted for cross-protection, that is, the protection that vaccination against or natural infection by a B lineage offers against the opposite B lineage. A more detailed description of the dynamic model and main input parameters can be found in Supplemental document A and Appendix Table 1 in the Supplemental Materials.

For the economic model, we used an age-structured decision tree model (Fig. 1), developed in Excel 2010 and linked to the dynamic model described above. The output of the dynamic model, age-stratified symptomatic influenza cases, served as input to the economic model. First, the age groups of the dynamic model were recategorized in the economic model to align with available data on economic parameters (0–23 months, 2 years, 3–4 years, 5–11 years, 12–17 years, 18–49 years, 50–64 years, 65+ years), using age-distribution data of the US population [16]. Next, the economic model stratified influenza cases between non–high risk (NHR) patients and high risk (HR) patients on the basis of the presence of chronic disease [17]. Then, cases were divided into four categories (no medical attention, outpatient visit, hospital admission, and death) on the basis of relevant medical complication probabilities reported by Molinari et al. [4]. For children younger than 18 years, outpatient visits were further subdivided between uncomplicated cases, cases with otitis media, and cases with pneumonia/other complication following the model design of Prosser et al. [18]. We ignored the adverse events of vaccine in our model because the safety profile of TIV and QIV was

found to be similar [19–21].

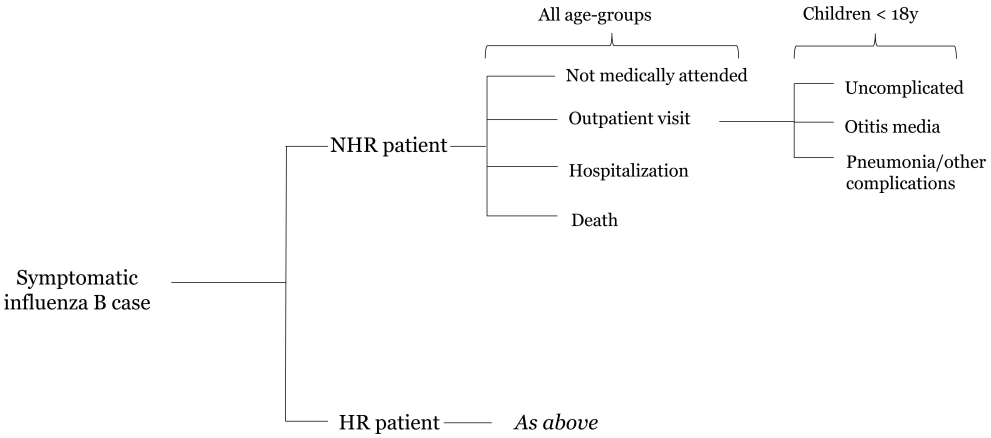

Fig. 1: Flow diagram of the economic decision tree model. NHR: Non-high risk, HR: High risk.

2.3. Probabilities

Table 1 lists all relevant probabilities included in the model.

2.3.1. Health status

Age-specific proportions of the US population at high risk of complications were derived from Molinari et al. [4]. HR statuses were based on the Advisory Committee on Immunization Practices recommended groups for influenza vaccination [22]. Notably, being 65 years or older was not sufficient on its own for an individual to qualify as being at high risk. Because the dynamic transmission model did not stratify by health status, we divided the symptomatic influenza cases between HR and NHR according to the prevalence of HR in the different age groups. This assumes that HR and NHR patients were at equal risk of influenza infection and of developing symptomatic influenza. To correct for difference in vaccination coverage between HR and NHR (higher in the HR group), we adjusted the division of influenza cases between NHR and HR according to NHR-/HR-specific vaccination coverages [23,24].

2.3.2 Primary care

The probability of an outpatient visit per influenza B case was based on published studies [4,18]. In these studies, it was assumed that the probability of an outpatient visit for an HR patient was estimated to be approximately twice that of an NHR patient, except for elderly, where the corresponding factor was estimated at 1.3. For children, outpatient visits were further divided between uncomplicated cases and complicated cases, which were defined as cases presenting with otitis media and pneumonia/other complications [18].

2.3.3 Hospitalizations and mortality

Consistent with primary care data source, probabilities of hospitalization and death were derived from the same source [4]. These probabilities were based on 1980-2001 data and estimated by modeling excess hospitalizations and deaths using International Classification of Diseases-9 codes for underlying respiratory and circulatory conditions. No distinction between risk groups was available here, so this was not included in the base-case analysis. However, a scenario with higher probability of hospitalization and death for HR individuals was explored in the sensitivity analysis.

2.4. Costs

2.4.1. Medical costs

Costs are presented in Table 1 and adjusted to 2013 US dollars using the Consumer Price Index [25]. All medical costs were derived from published US studies. Cost data of outpatient visits included outpatient service claims as well as pharmaceutical claims and laboratory testing [4,18]. For children, costs of a hospitalization included diagnostics, therapeutics (including prescriptions), room costs, and physician services [18,26]. For adults, total costs of hospitalized patients and deaths were based on all direct costs of 2 weeks before admission to 30 days after admission, including inpatient costs, outpatients cost, and pharmaceutical claims [4]. Notably, the assumption was that all patients dying received some hospital care before they died. Costs of over-the-counter medication were retrieved from published sources [4,18,27], and counted for all influenza cases, including cases that did not seek medical attention.

2.4.2. Vaccination costs

Total yearly number of administered vaccinations was calculated by multiplying the age-specific coverage rates with the corresponding population sizes, as already present in the underlying dynamic model. The Advisory Committee on Immunization Practices recommends that children younger than 8 years receiving influenza vaccination for the first time should be vaccinated twice, although this advice is likely not strictly adhered to [22]. As such, and in accordance with previous modeling studies, the number of vaccines given to children aged 6 to 23 months, 2 years, and 3 to 4 years was multiplied by 2, 1.5, and 1.33, respectively [18]. Vaccine prices of TIV and QIV for the public and private markets were obtained from the CDC vaccine price list of 2013 [28]. We assumed that 50% of children younger than 12 years, 30% of adolescents aged between 12 and 18 years, and 10% of the adults obtain the vaccine funded under the public price and the remainder by paying private market prices [29]. No administration costs were included in this analysis because these were assumed to be equal in both alternatives.

2.4.3. Indirect costs

Age- and health-status–specific productivity losses were derived from Molinari et al. [4]. Up to the age of 17 years, lost productivity was counted as parental work loss, whereas for cases 18+ years old work loss was assigned to the cases themselves. Following the US Panel on Cost Effectiveness in Health and Medicine, we used the friction costs method approach to count productivity losses [30]. This approach limits productivity losses of long-term absence to a friction period, assuming that employees have been replaced after this initial period [31]. The friction period was set at 40 days, which comprises 20 days to make the decision whether an employee has to be replaced and another 20 days to fill the vacancy [32,33]. In line with the friction costs method, we multiplied the number of workdays lost with the elasticity adjustment factor, as the proportion of reduction in effective labor time due to absence will be less than 1 due to, for example, a company's internal labor reserves [34]. Because we were not able to identify data on US elasticity of labor, as such, we used an internationally suggested elasticity of 0.8 [35]. Finally, adjusted productivity losses were calculated by multiplying the lost productivity days with age-specific daily earnings [36]. These daily earnings were further adjusted for age-specific labor participation rates [16]. For productivity losses of caregivers, we used average daily earnings of the age group 25 to 54 years.

2.5. Health Effects

QALY losses of influenza and its complications are presented in Table 1. For children younger than 18 years, QALY loss for uncomplicated influenza was estimated at 0.005 per episode [37]. This was based on time trade-off questions for parents on uncomplicated influenza of their child. Additional QALY losses for children with otitis media, pneumonia, and hospitalized influenza were derived from a pneumococcal study, and were estimated at 0.042, 0.046, and 0.076, respectively [38]. QALY loss of a non-hospitalized influenza episode in the adult population was estimated at 0.0071 [39,40]. This was based on pooled patient-level data from four clinical trials in which data on quality of life (QOL) of ambulatory patients with laboratory-confirmed influenza were collected for 7 days using the visual analogue scale score [40]. The QALY loss of an adult with influenza-related hospitalization was estimated to be 1.8 times higher than that of an ambulatory patient on the basis of a QOL assessment among patients with clinically diagnosed influenza in Belgium using the standardized 12-Item Short Form Survey (SF-12)[41]. The number of LYs lost because of influenza-related deaths was calculated by estimating remaining life expectancies at the age of death using life tables [42]. LYs were transformed to QALYs by adjusting these with baseline age-specific QOL estimates [43].

Table 1 – Input of the economic model.

Variable		Base case	DSA range	Type of distribution	Ref.
Outcome probabilities					
Proportion at HR of serious complications					
0-4 yrs		0.052	NA	NA	
5-17 yrs		0.106	NA	NA	
18-49 yrs		0.149	NA	NA	[4]
50-64 yrs		0.330	NA	NA	
65+ yrs		0.512	NA	NA	
Probability of outpatient visit/flu infection					
0-1 yrs:	NHR HR	0.50 1	0.17-0.83 2 x NHR	Beta(3.9;3.9) 1.8 x NHR	
2 yrs:	NHR HR	0.47 0.94	0.15-0.81 2 x NHR	Beta(3.7;4.1) 1.9 x NHR	
3-4 yrs	NHR HR	0.43 0.86	0.12-0.78 2 x NHR	Beta(3.3;4.4) 2.1 x NHR	[18]
5-11 yrs	NHR HR	0.28 0.56	0.11-0.50 2 x NHR	Beta(5.4;14) 2 x NHR	
12-17 yrs	NHR HR	0.24 0.48	0.06-0.50 2 x NHR	Beta(3.2;10) 2 x NHR	
18-49 yrs	NHR HR	0.31 0.62	0.28-0.34 2 x NHR	Beta(338;752) 2 x NHR	
50-64 yrs	NHR HR	0.31 0.62	0.28-0.34 2 x NHR	Beta(338;752) 2 x NHR	[4]
65+ yrs	NHR HR	0.62 0.82	0.57-0.67 1.3 x NHR	Beta(200;122) 1.3 x NHR	
Probability of otitis media / influenza related outpatient visit					
0-1 yrs	All-risk	0.63	0.33-0.80	Beta(9.6;5.6)	
2 yrs	All-risk	0.58	0.27-0.80	Beta(7.2;5.2)	
3-4 yrs	All-risk	0.39	0.17-0.60	Beta(7.3;11)	[18]
5-11 yrs	All-risk	0.23	0.05-0.50	Beta(2.9;9.6)	
12-17 yrs	All-risk	0.15	0.01-0.40	Beta(1.8;10)	
Probability of pneumonia or other complication / influenza related outpatient visit					
0-1 yrs	All-risk	0.20	0.04-0.5	Beta(2.1;8.5)	
2 yrs	All-risk	0.15	0.02-0.4	Beta(1.9;11)	
3-4 yrs	All-risk	0.15	0.02-0.4	Beta(1.9;11)	[18]
5-11 yrs	All-risk	0.11	0.02-0.3	Beta(2.0;16)	
12-17 yrs	All-risk	0.08	0.01-02	Beta(2.4;28)	

Table 1 – Input of the economic model (*continued*).

Variable		Base case	DSA range	Type of distribution	Ref.
Probability of hospitalization / flu case					
0-4 yrs	All-risk	0.0141	0.0049-0.0233	Beta(8.9;619)	
5-17 yrs	All-risk	0.0006	0.0002-0.001	Beta(9.0;14981)	
18-49 yrs	All-risk	0.0042	0.0015-0.0069	Beta(9.0;2124)	[4]
50-64 yrs	All-risk	0.0193	0.00676-0.0318	Beta(8.9;452)	
65+ yrs	All-risk	0.0421	0.0147-0.0695	Beta(8.6;196)	
Probability of death / flu case					
0-4 yrs	All-risk	0.00004	0.00002-0.00006	Beta(16;399967)	
5-17 yrs	All-risk	0.00001	0.000008-0.000012	Beta(100;9999799)	
18-49 yrs	All-risk	0.00009	0.00003-0.00015	Beta(9;99981)	[4]
50-64 yrs	All-risk	0.00134	0.000458-0.00222	Beta(8.9;6599)	
65+ yrs	All-risk	0.0117	0.00406-0.0193	Beta(8.9;750)	
Costs (2013 US$)					
Outpatient visit without complication					
0-17 yrs	All-risk	46	12-119	Lognormal(3.8;0.6)	[18]
Outpatient visit otitis media					
0-1 yrs	All-risk	106	31-270	Lognormal(4.7;0.55)	
2-4 yrs	All-risk	114	31-275	Lognormal(4.7;0.55)	[18]
5-17 yrs	All-risk	129	42-337	Lognormal(4.9;0.53)	
Outpatient visit pneumonia or other complication					
0-1 yrs	All-risk	246	85-983	Lognormal(5.5;0.63)	
2-4 yrs	All-risk	122	38-458	Lognormal(4.8;0.64)	[18]
5-17 yrs	All-risk	150	97-691	Lognormal(5.0;0.50)	
Outpatient visit					
18-49 yrs	NHR HR	158 918	149-168 854-985	Lognormal(5.0;0.03) Lognormal(6.8;0.036)	
50-64 yrs	NHR HR	190 928	171-210 895-962	Lognormal(5.2;0.04) Lognormal(6.8;0.018)	[4]
65+ yrs	NHR HR	306 603	279-335 586-620	Lognormal(5.7;0.03) Lognormal(6.4;0.015)	
Hospitalization					
0-1 yrs	NHR HR	7,650 9,835	6,314-8,985 2,550-28,667	Lognormal(8.9;0.090) Lognormal(9.2;0.62)	
2 yrs	NHR HR	6,193 9,107	3,036-14,813 3,278-41,769	Lognormal(8.7;0.40) Lognormal(9.1;0.65)	
3-4 yrs	NHR HR	6,678 12,385	2,671-15,057 3,278-41,769	Lognormal(8.8;0.4) Lognormal(9.4;0.65)	[18]
5-17 yrs	NHR HR	7,770 10,443	485-43,348 2,671-62,775	Lognormal(9.0;1.1) Lognormal(9.3;0.81)	

Table 1 – Input of the economic model (*continued*).

Variable		Base case	DSA range	Type of distribution	Ref.
18-49 yrs	NHR	24,076	15,229-36,229	Lognormal(10;0.22)	
	HR	60,419	40,398-86,971	Lognormal(11;0.20)	
50-64 yrs	NHR	28,245	16,957-44,288	Lognormal(10;0.24)	[4]
	HR	52,300	45,058-60,369	Lognormal(11;0.075)	
65+ yrs	NHR	14,501	11,972-17,398	Lognormal(9.6;0.095)	
	HR	21,207	19,554-22,960	Lognormal(10;0.041)	
Medical cost per death					
0-17 yrs	NHR	36,486	16,985-68,971	Lognormal(10;0.36)	
	HR	339,249	66,379-1,054,158	Lognormal(12;0.71)	
18-49 yrs	NHR	96,647	19,663-294,799	Lognormal(11;0.69)	
	HR	96,082	25,337-256,950	Lognormal(11;0.59)	[4]
50-64 yrs	NHR	150,124	41,801-389,784	Lognormal(12;0.57)	
	HR	150,462	58,406-320,894	Lognormal(12;0.43)	
65+ yrs	NHR	53,109	34,851-77,625	Lognormal(11;0.20)	
	HR	41,794	35,909-48,365	Lognormal(11;0.076)	
OTC medication					
0-2 yrs	All-risk	3.3	1.7-6.6	Lognormal(1.2;0.35)	
3-4 yrs	All-risk	4.9	2.5-10	Lognormal(1.6;0.35)	
5-11 yrs	All-risk	6.5	3.3-13	Lognormal(1.9;0.35)	[4,18, 27]
12-17 yrs	All-risk	3.0	1.5-6.1	Lognormal(1.1;0.35)	
18+ yrs	All-risk	3.8	1.0-10	Lognormal(1.2;0.61)	
Lost work days: No complication*					
0-4 yrs	All-risk	1	0.50-1.5	Gamma(3.8;0.26)	
5-17 yrs	All-risk	0.5	0.25-0.75	Gamma(3.8;0.13)	
18-49 yrs	All-risk	0.5	0.25-0.75	Gamma(3.8;0.13)	[4]
50-64 yrs	All-risk	0.5	0.25-0.75	Gamma(3.8;0.13)	
65+ yrs	All-risk	1	0.50-1.5	Gamma(3.8;0.26)	
Lost work days: Outpatient visit*					
0-4 yrs	NHR	1	0.50-1.5	Gamma(3.8;0.26)	
	HR	6	3.0-9.0	Gamma(3.8;1.6)	
5-17 yrs	NHR	1	0.50-1.5	Gamma(3.8;0.26)	
	HR	4	2.0-6.0	Gamma(3.8;1.0)	
18-49 yrs	NHR	1	0.50-1.5	Gamma(3.8;0.26)	[4]
	HR	2	1.0-3.0	Gamma(3.8;0.52)	
50-64 yrs	NHR	2	1.0-3.0	Gamma(3.8;0.52)	
	HR	4	2.0-6.0	Gamma(3.8;1.0)	
65+ yrs	NHR	3	1.5-4.5	Gamma(3.8;0.78)	
	HR	7	3.5-11	Gamma(7;1.8)	

Table 1 – Input of the economic model (*continued*).

Variable		Base case	DSA range	Type of distribution	Ref.
Lost work days: Hospitalization*					
0-4 yrs	NHR	8	4.0-12	Gamma(3.8;2.1)	[4]
	HR	31	16-47	Gamma(31;8.1)	
5-17 yrs	NHR	9	4.5-14	Gamma(3.8;2.3)	
	HR	23	12-35	Gamma(23;6.0)	
18-49 yrs	NHR	12	6.0-18	Gamma(3.8;3.1)	
	HR	21	11-32	Gamma(21;5.5)	
50-64 yrs	NHR	13	6.5-20	Gamma (3.8;3.4)	
	HR	24	12-36	Gamma (24;6.2)	
65+ yrs	NHR	13	6.5-20	Gamma (3.8;3.4)	
	HR	18	9.0-27	Gamma (18;4.7)	
Cost of lost workday					
18-49 yrs	All-risk	83	NA	NA	[16,36]
50-64 yrs	All-risk	86	NA	NA	
65-75 yrs	All-risk	12	NA	NA	
Caregiver	All-risk	93	NA	NA	
Incremental vaccine price					
6mo-11y		5.43	NA	NA	[28,29]
12y-17y		5.44	NA	NA	
>18y		5.36	NA	NA	
Health effects					
QALY loss children < 18 years					
Episode of influenza, uncomplicated	All-risk	0.005	0.002-0.009	Gamma(7.8;0.00064)	[37]
Episode of otitis media	All-risk	0.042	0.023-0.065	Gamma(15;0.0027)	[38]
Episode of pneumonia or other hospitalized complication	All-risk	0.046	0.027-0.071	Gamma(17;0.0027)	
Hospitalization for pneumonia or other respiratory condition due to influenza	All-risk	0.076	0.054-0.100	Gamma(42;0.0018)	
QALY loss adults					
Episode of influenza, uncomplicated	All-risk	0.007	0.0054 – 0.0086	Normal(0.007;0.0008)	[40]
Hospitalized influenza	All-risk	0.013	0.010 – 0.016	Normal(0.013;0.0015)	[40,41]

* A range of deterministic value ± 50% was used as 95% confidence interval. DSA: Deterministic sensitivity analysis, HR: High risk, NHR: Non-high risk, Yrs: Years

2.6. Cost-Effectiveness

A time horizon of 20 years was used (week 30 of 2014 to week 29 of 2034) to cover fluctuations in influenza disease between seasons regarding, for example, attack rate, dominant strains, and vaccine mismatches. Cumulative direct costs, indirect costs, LYs lost, and QALYs lost were determined for both alternative vaccines over the full time horizon. The incremental cost-effectiveness ratios (ICERs) of shifting from TIV to QIV were then calculated by dividing the net difference in costs by the net difference in QALYs or LYs. To take time preferences into account, future costs and health effects were annually discounted at a rate of 3% [30].

2.7. Sensitivity Analysis

A deterministic sensitivity analysis was performed to vary to the upper and lower bounds of the 95% confidence interval (CI) parameters considered of main interest (Table 1). For probabilities and costs derived from Prosser et al. [18], we interpreted the presented ranges as 95% CIs. SDs of costs derived from Molinari et al. [4] were used to estimate 95% CIs. Results of the deterministic sensitivity analysis were presented in a tornado diagram.

Scenario analysis was performed to explore the effect of alternative plausible inputs on cost-effectiveness outcomes. Concerning parameters of the dynamic model, vaccine efficacy (range -20% to +20% of base-case efficacy), vaccine coverage (range -20% to +20% of base-case coverage), cross-protection against opposite B lineage (range 40%–95% of matched vaccine efficacy), and duration of natural protection (6–18 years) were explored. For the economic model, there were higher risks of hospitalization and mortality for the HR group than for the NHR group [44–46]. Concerning health effects, alternative QALY loss assumptions as estimated by Sander et al. [47] were explored in the model. Also, assumptions on calculations of the productivity losses were varied by excluding the elasticity of adjustment factor and increasing the friction period to 23 weeks, according to Dutch cost-effectiveness guidelines [32], and a scenario using the human capital approach. Here, lost earnings in all remaining LYs till retirement were counted, ranging from $235,294 for the age group of 65+ years to $1,739,727 for the age group of 18 to 49 years [4]. Finally, discount rates were varied, using 5% for both costs and health effects and a scenario with 3% for costs and 0% for health effects.

A probabilistic sensitivity analysis (PSA) was performed to analyze the robustness of the results. Parameters of the dynamic model involved in the PSA were probability of influenza infection (β) with B Yamagata and B Victoria, cross-protection due to natural infection and due to vaccination, duration of protection after natural infection, weight of seasonal forcing,

and duration of the infectious period. Sampling was performed from the estimated posterior distributions of the listed parameters whose 95% high-density intervals are given in Table 1. In addition, plots of the posterior of these parameters are given in the Supplemental Materials (see Appendix Fig. 1 in Supplemental Materials). Parameter distributions in the economic model were defined using means and SDs as presented in Table 1. A total of 1000 iterations were done and for each combination of parameters, the results were presented in a cost-effectiveness plane. A cost-effectiveness acceptability curve was generated to show the proportion of cost-effective simulations over a range of willingness-to-pay thresholds.

3. Results

3.1. Health Outcomes, Costs, and Cost-Effectiveness

The impact of shifting from TIV to QIV on health outcomes and costs is presented in Table 2. Over the next 20 years, shifting to QIV will decrease the number of influenza B cases by 16.0 million (27.2%). Annual average numbers of prevented influenza B cases by age group can be found in Appendix Table 2 in Supplemental Materials. Consequently, this will avoid 6.1 million outpatient visits, 137,645 hospitalizations, and 16,199 deaths, a reduction of 29.4%, 30.4%, and 31.7%, respectively. In addition, a total of 99,558 QALYs will be gained because of reduced influenza illness and 113,190 QALYs because of averted influenza deaths. Concerning costs, shifting to QIV leads to an increase of $11.6 billion in vaccine costs; however, $1.5 billion in outpatient visit costs, $2.5 billion in hospitalization costs, and $0.8 billion in costs of influenza-related deaths would be saved. From the societal perspective, an additional $0.8 billion of productivity losses and $0.05 billion in over-the-counter medication costs are estimated to be saved. Table 3 presents the incremental costs, health effects, and ICERs of QIV versus TIV. The incremental costs of shifting from TIV to QIV are $6.7 billion and $5.8 billion from the TPP perspective and the societal perspective, respectively. Consequently, a total of 212,722 QALYs and 143.7 LYs will be gained. This results in ICERs of $31,385/QALY gained from the TPP perspective and $27,411/QALY gained from the societal perspective. Regarding LYs, the ICER is $46,477 per LY gained (TPP) and $40.591 per LY gained (societal).

3.2. Univariate Sensitivity Analysis

The deterministic sensitivity analysis shows that the ICER was most sensitive to the probability of death (Fig. 2A). Two further parameters with high impact on the ICER were the probabilities of hospitalization and the QALY losses attributed to influenza illness. The scenario analysis demonstrated that the ICER was most sensitive to the level of cross-protection (Fig. 2B). Decreasing the cross-protection from 70% to 40% of vaccine efficacy changed the ICER to cost saving, whereas increasing the cross-protection to 95% of vaccine effica-

cy resulted in an ICER of $297,000/QALY gained. Quantifying productivity losses using the human capital approach instead of friction methods approach decreased the ICER to $15,000/QALY gained. When QALY losses due to influenza illness were used as presented by Sander et al. [47], the ICER decreased to $15,700/QALY gained. Altering the incremental vaccine price of QIV over TIV 25% downward and upward resulted in ICERs of $13,840 and $40,991/ QALY gained, respectively. A threshold analysis estimated that an incremental price of $7.63 rendered an ICER equal to $50,000/QALY gained.

Extended results of the univariate analysis of the most influential parameters, cross-protection of vaccine efficacy against matched strain and vaccine efficacy, is presented in Figure 2. Cost-saving ICERs were obtained when cross-protection was 50% or less of the vaccine efficacy (Fig. 2C). Variation of the vaccine efficacy within ±20% of the base-case value resulted in an ICER ranging between $10,983 and 35,620/QALY gained (Fig. 2D).

Table 2: Health outcomes and costs of replacement of TIV by QIV in the United States over the next 20 years (2014-2034). Costs and health effects discounted at 3%.

Outcomes	TIV	QIV	Difference
Clinical outcomes			
Total number of symptomatic B cases (input from dynamic transmission model)	54,752,913	38,769,820	-15,983,094
Total number of patients with outpatient visit	20,765,647	14,659,055	-6,106,592
Total number of hospitalizations	452,440	314,795	-137,645
Total number of deaths	51,118	34,919	-16,199
Health effects			
Total QALYs lost due to influenza illness	324,533	224,975	-99,558
Total QALYs lost due to influenza-related death	348,694	235,504	-113,190
Total life years lost due to influenza-related death	441,894	298,227	-143,667
Costs ($)			
Vaccination	21,533,371,885	33,084,640,683	11,551,268,798
Outpatient visit	5,047,241,705	3,499,717,979	-1,547,523,725
Hospitalized	8,065,030,717	5,538,868,166	-2,526,162,550
Death	2,461,272,640	1,660,860,902	-800,411,738
Productivity losses	2,593,650,999	1,797,327,693	-796,323,306
OTC medications	161,308,724	112,012,536	-49,296,188

TIV: Trivalent influenza vaccine, QIV: Quadrivalent influenza vaccine, QALY: Quality-adjusted life year, OTC: Over the counter

Table 3: Incremental cost-effectiveness results. Numbers include a discount rate of 3% unless otherwise stated.

Outcomes	TIV	QIV	Incremental
Total health care costs ($)	37,106,916,946	43,784,087,731	6,677,170,784
Total health care costs ($) (undiscounted)	49,312,653,802	58,204,478,071	8,891,824,269
Total health care costs + societal costs ($)	39,861,876,669	45,693,427,960	5,831,551,291
Total health care costs + societal costs ($) (undiscounted)	53,012,885,962	60,815,765,930	7,802,879,968
Total QALY loss	673,227	460,480	-212,748
Total QALY loss (undiscounted)	1,092,072	760,040	-332,032
Life years loss	441,894	298,227	-143,667
Life years loss (undiscounted)	833,130	573,936	-259,194
ICER ($/QALY gained)			
TPP perspective	-	-	31,385
TPP perspective (undiscounted)	-	-	26,780
Societal perspective	-	-	27,411
Societal perspective (undiscounted)	-	-	23,500
ICER ($/life year gained)			
TPP perspective			46,477
TPP perspective (undiscounted)			34,306
Societal perspective			40,591
Societal perspective (undiscounted)			30,104

TIV: Trivalent influenza vaccine, QIV: Quadrivalent influenza vaccine, QALY: Quality-adjusted life year, ICER: Incremental cost-effectiveness ratio, TPP: Third-party-payer

3.3. Probabilistic Sensitivity Analysis

The PSA demonstrated that the cost-effectiveness results are robustly scattered in the north-eastern quadrant of the cost-effectiveness plane (Fig. 3A). The PSA demonstrated that 97.2% and 100% of the simulations were cost-effective from the societal perspective using a willingness-to-pay threshold of $50,000/QALY gained and $100,000/QALY gained, respectively (Fig. 3B). From the TPP perspective, these proportions were 94.6% and 100%, respectively.

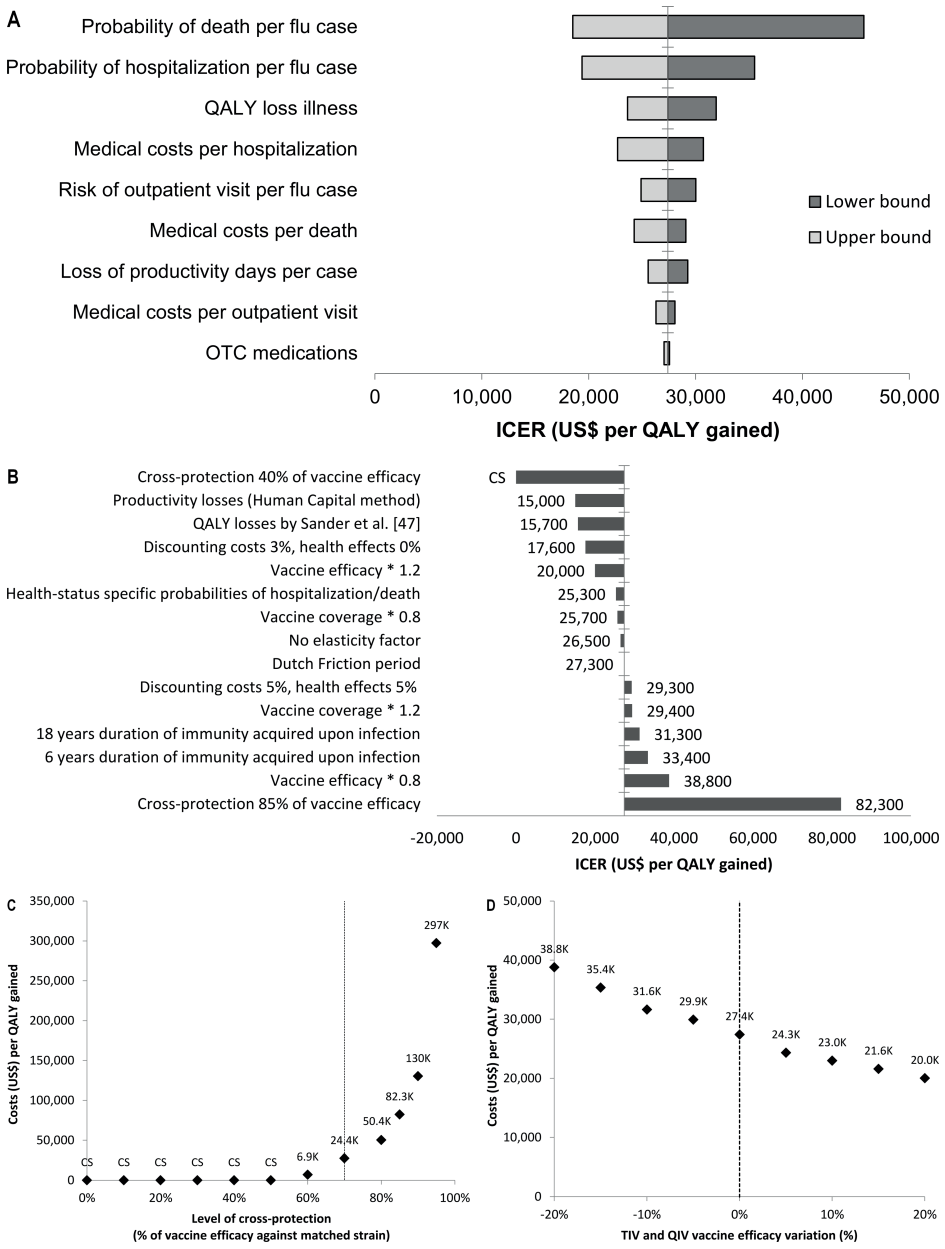

Fig. 2: Univariate sensitivity analysis using the societal perspective. (A) Deterministic sensitivity analysis. Parameters were varied within their 95% confidence intervals. (B) Scenario analysis using the societal perspective. The y-axis shows the various scenarios explored in the model. A 85% cross-protection was shown instead of 95% cross-protection in order to improve readability of the figure (shown with asterisk). Using 95% cross-protection, the ICER was US $297,000/QALY gained. (C) Univariate sensitivity analysis of the level of cross-protection. (D) Univariate sensitivity analysis of the level of vaccine efficacy. ICER, incremental cost-effectiveness ratio, OTC, over-the-counter, QALY, quality-adjusted life-year.

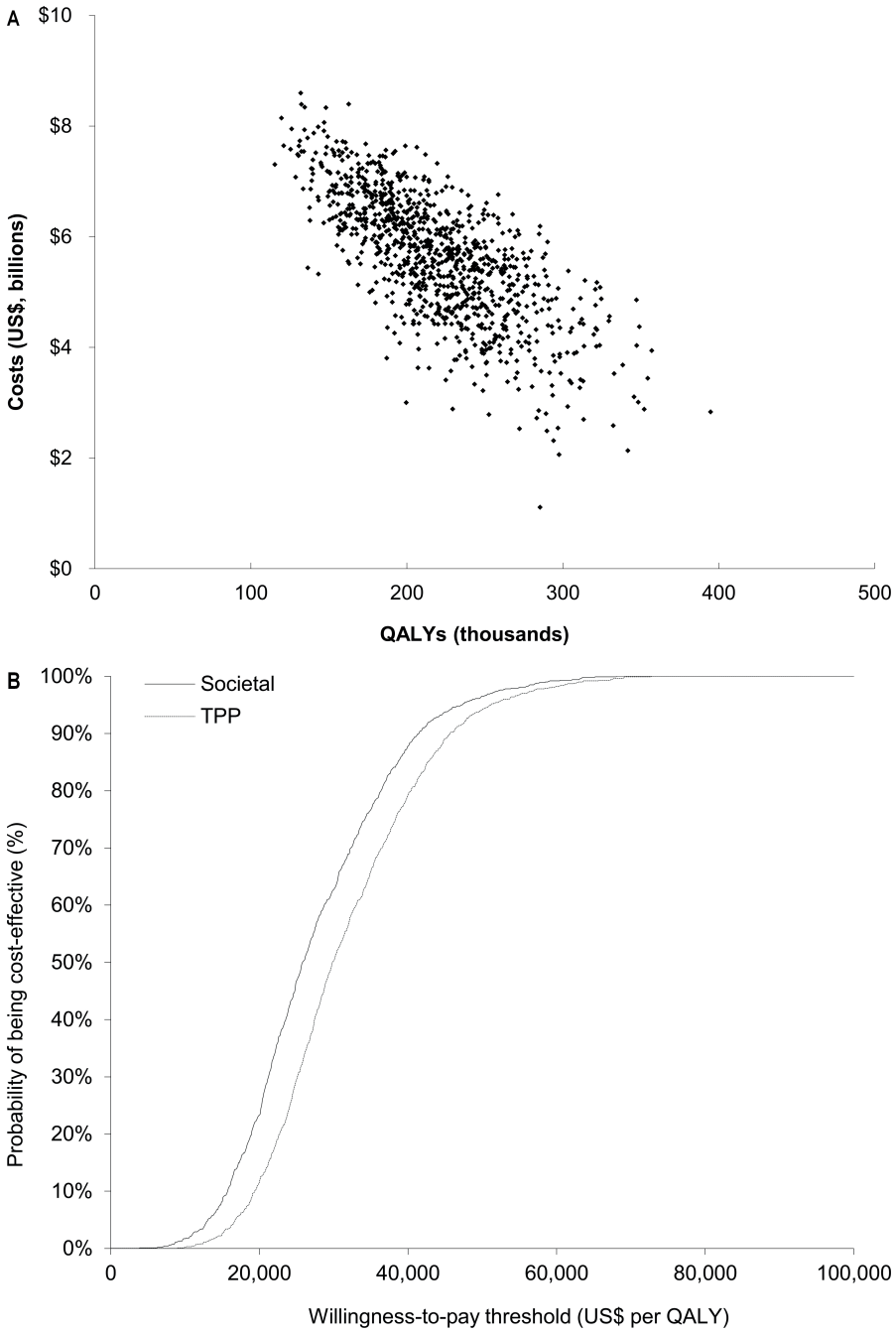

Fig. 3: Probabilistic sensitivity analysis of quadrivalent influenza vaccine versus trivalent influenza vaccine over a time period of 20 years (1000 simulations). (A) Cost-effectiveness plane of the societal perspective. Third-party payer's (TPP's) perspective was not shown because of a high level of overlap. (B) Cost-effectiveness acceptability curve of the societal perspective (normal line) and the TPP perspective (dashed line).

4. Discussion

Our results indicate that shifting from TIV to QIV is expected to reduce the health burden of influenza B over the next 20 years by 27.2% (16.0 million influenza B cases) in the US. This would prevent 6.1 million outpatient visits, 137,645 hospitalizations, and 16,199 deaths. Moreover, our analysis has demonstrated that QIV is a cost-effective alternative, with ICERs of $31,385 and $27,411/QALY gained from the TPP perspective and the societal perspective, respectively. The PSA showed that the results were robust, given that more than 94% of the simulations were below a threshold of $50,000/QALY gained and all simulations were below $100,000/QALY gained. Variables with a high impact on the ICER were level of cross-protection against opposite B lineage, vaccine efficacy, vaccine price, and probability of death given symptomatic influenza.

So far, two economic comparisons of QIV versus TIV in the US have been conducted, involving a cost-benefit [10,11] and a cost-effectiveness analysis [12]. The cost-benefit analysis used data on clinical outcomes (symptomatic cases, hospitalizations, and deaths) from a retrospective study by Reed et al. [9]. This study, using a static model, estimated that during the seasons 1999-2000 to 2008-2009 QIV could have reduced the number of influenza cases on average by 342,700 per year, resulting in annual reductions of 2,144 hospitalizations and 137 deaths [9]. Our dynamic model estimated the number of prevented influenza cases to be more than twice as high (mean yearly reduction of 799,155 influenza cases), which might be at least partly explained by our model's ability to account for herd immunity. Other differences as compared with Reed et al. [9] are that our analysis is age-stratified and takes into account the existing population immunity and cross-protection against the mismatched B strain. Regarding health-related outcomes, it is striking that our estimate on the number of influenza deaths is relatively high as compared with Reed et al. [9] (810 vs. 137). This might be related to the fact that we used influenza-related mortality estimates based on International Classification of Diseases-9 codes of all underlying respiratory and circulatory diseases, whereas Reed et al. [9] restricted the analysis to only those causes of death corresponding to International Classification of Diseases-9 codes of influenza and pneumonia only. Because it has previously been suggested that including only respiratory categories might result in an underestimation of deaths attributed to influenza [48], we chose to use mortality estimates that included all underlying respiratory and circulatory diseases. The corresponding cost-benefit analysis by Lee et al. [10,11] estimated the mean incremental costs per influenza case averted at $1218, using the TPP perspective and an incremental vaccine price of $5. Applying exactly the same vaccine price difference, we estimated a lower incremental cost per case of $488. This might be related to the higher hospitalization costs used in our analysis, although we had no access to specified cost data of the study of Lee et al. [10,11].

The second economic analysis comparing QIV with TIV in the US was a cost-effectiveness analysis by Clements et al. [12]. This study also used a static approach and estimates on influenza incidence, vaccine efficacy, and cross-protection, which were similar to ours. Despite the different modeling approach, we found similar reductions in hospitalizations and deaths. Moreover, the incremental costs of QIV over TIV were comparable from a TPP perspective ($340 million by Clements et al. [12] vs. $445 million in our study [undiscounted]) and even closer from a societal perspective ($327 million by Clements et al. [12] vs. $390 million in our study [undiscounted, productivity losses of death excluded for consistency]). Because Clements et al. [12] did not account for herd protection and did not count QALY losses due to influenza illness, but only due to deaths, we found a higher QALY gain in our study (9584 vs. 3593). This explains our lower estimated cost-effectiveness ratio of $27,415/QALY gained as compared with the one by Clements et al. [12] ($90,301/QALY gained). A comparison of QIV with TIV in the United Kingdom found an ICER of €27,378/QALY gained ($44,300) for the TPP perspective, which is also in the range of what we found [49]. Important differences to our analysis are the static approach they used.

A strong point of this study was the use of a dynamic transmission model, which provides the ability to account for changes in the force of infection arising from the reduction in the prevalence of infected individuals brought about by vaccination. Static models, in contrast, use a fixed force of infection, which makes them able to capture only the impact of direct protection at the very start of an influenza season. As soon as direct protection of vaccination influences the prevalence of infectious cases, a change in the force of infection occurs. Static models then cease to quantify the direct protection of vaccination correctly, making the value of a direct comparison between the static and dynamic modeling approaches of limited value only. Moreover, because the force of infection influences the direct and indirect impact of the vaccination in our analytic context, this comparison is further hampered. Yet, if comparing static and dynamic models, the most valid comparison might be between Reed et al. [9] (as already discussed above) and results of our dynamic model previously shown in Crepey et al. [15], because these studies cover the same time period (2001–2009). This comparison shows that in this situation the dynamic model predicted twice the number of influenza cases prevented per year as compared with the static model (342,700 vs. 661,600).

As with any economic evaluation, our analysis is a simplification of the real world and we had to make some assumptions. One simplification of our model structure concerned the exclusion of the use of antiviral medication (such as zanamivir and oseltamivir). However, the efficacy of antiviral medication was included intrinsically in the probabilities of influenza-related complications we used, as well as the costs of antiviral medications (including the "older" drugs amantadine and rimantidine) that were included in the cost data of outpatient

visits. Because these cost data were based on the period 2001-2003, prescription behavior may have changed in the meantime and could therefore have an impact on our results. We expect this impact to be small, however, because the univariate sensitivity analysis showed that the outpatient visits' costs had a minor impact on the ICER. Second, we used probabilities of complications, cost estimates, and QALY losses of influenza in general, because data specific to influenza type B were scarce. However, literature so far did not show significant differences in clinical burden between influenza A and influenza B [50]. Furthermore, estimates on probabilities to a clinical event stratified between HR and NHR population were scarce. Therefore, the influenza-related probabilities of outpatient visits for HR populations had to be based on assumptions taken from earlier studies [4,18]. For the probability of hospitalization and death, we applied the same risk for the HR population as for the NHR population, in the absence of data. Because HR individuals tend to have a higher risk of hospitalization or death [45,46,51] and higher treatment costs [4], our assumptions can be considered as conservative in this regard. Also, we did not explicitly take into account potential vaccination with live-attenuated influenza vaccine (LAIV) in our model. The current Advisory Committee on Immunization Practices recommendations do however not prefer LAIVs over inactivated influenza vaccines because efficacy estimates were found to be similar [52]. Concerning costs, incremental vaccine costs of QIV over TIV were based on inactivated vaccine price differences, whereas the CDC list-price of trivalent-LAIV and quadrivalent-LAIV remained the same [53,54]. This might result in an overestimation of the incremental vaccine costs of QIV over TIV, which can therefore be regarded as a conservative approach in our analysis. Finally, we assumed a complete one-off switch from TIV to QIV for all age groups, whereas in reality this switch might be gradual. However, adoption of QIV in the US has been widespread, although no public data by age group are available at the moment. Moreover, full-scale adoption of QIV might again be considered a conservative approach for estimating the ICER as compared with targeted adoption.

No official willingness-to-pay threshold exists for the US; however, $50,000/QALY gained has been cited in most articles [55]. Our study demonstrates that shifting to QIV would be a cost-effective intervention in the base case applying this threshold. Another approach, which has recently been proposed by the World Health Organization, is to relate the cost-effectiveness threshold to other health program alternatives to judge whether an intervention offers good value for the health care budget [56]. In the US, multiple vaccines have been added to the CDC's vaccination schedule during the last decade. Examples of these recommended vaccines and their cost-effectiveness are pneumococcal conjugate vaccine for 65+-year-olds (ICER $62,065/QALY) [57], tetanus toxoid, diphtheria toxoid and acellular pertussis for 65+-year-olds ($13,000–$328,000/QALY) and for pregnant women ($414,523/QALY) [58,59], meningococcal conjugate vaccine for 11-year-olds + catch-up 10- to 17-year-olds

($88,000/QALY) [60], and human papillomavirus for 12-year-old girls ($3,000–45,000/QALY) and for 12-year-old boys ($20,000– 250,000/QALY) [61]. The cost-effectiveness of QIV is at least as favorable as all aforementioned vaccines.

5. Conclusions

Our model estimates that replacement of TIV by QIV would reduce the number of influenza B cases by 27.2% (16 million cases) over the next 20 years in the US. This would avoid 6.1 million outpatient visits, 137,645 hospitalizations, and 16,199 deaths. In the base case, the ICER was estimated at $31,385/QALY gained from the TPP perspective and $27,411/QALY gained from the societal perspective. Sensitivity analyses demonstrate that the results are robust with similar cost-effectiveness results over various ranges of assumptions. QIV could be considered to be a cost-effective intervention from both the TPP perspective and the societal perspective applying a cost-effectiveness threshold of $50,000/QALY gained.

Supplemental Materials

Supplemental materials may be found here:
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